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CLINICAL REVIEW

Prevalence of sleep disturbances among head and neck cancer patients: A systematic review and meta-analysis

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SUMMARY

This systematic review and meta-analysis aim to investigate the prevalence rates of various types of sleep disturbances among head and neck cancer (HNC) patients before, during, and after cancer treatment. We performed a systematic search on PubMed, Embase, CINAHL, and PsycINFO to find studies that reported the prevalence of any type of sleep disturbance among adult HNC patients. Meta-analyses of prevalence were performed using random effects models, with I^2 values to indicate the extent of heterogeneity. In total, 29 studies of accumulatively 2315 HNC patients were included. The quality of the studies was fairly low and the heterogeneity was high. Studies on three types of sleep disturbances were found: insomnia (17 studies), hypersomnolence (12 studies), and sleep-related breathing disturbances (14 studies). The prevalence of insomnia was 29% (95% CI 20–41%) before treatment, 45% (95% CI 33–58%) during treatment, and 40% (95% CI 24–58%) after treatment, while for hypersomnolence the prevalence was 16% (95% CI 7–32%) before treatment and 32% (95% CI 20–48%) after treatment. The prevalence of sleep-related breathing disturbances before and after treatment was 66% (95% CI 44–82%) and 51% (95% CI 34–67%), respectively. These results imply that sleep disturbances are highly prevalent among HNC patients before, during, and after treatment.

Introduction

Every year more than half a million people in the world are diagnosed with head and neck cancer (HNC) [1]. Among this population, sleep disturbances have been hypothesized to be highly prevalent [2]. Two major risk factors of HNC, smoking and alcohol abuse [3], are associated with sleep disturbances in the general population [4,5]. Patients with HNC also often experience specific symptoms which may be associated with their disease and treatment phase, for example xerostomia (dry mouth) and pain in the mouth/throat area [6]. These symptoms are known to be strong predictors of sleep disturbances among HNC patients [7]. Moreover, being diagnosed with and treated for HNC is stressful. Previous studies have demonstrated that psychological distress including symptoms of anxiety and depression among HNC patients is highly prevalent [8,9] and is associated with sleep disturbances [10].

According to the third edition of the international classification of sleep disorders (ICSD-3), there are seven major diagnosis of sleep disorders: 1) insomnia, 2) sleep-related breathing disorders, 3) central disorders of hypersomnolence, 4) circadian rhythm sleep-wake disorders, 5) parasomnias, 6) sleep-related movement disorders, and 7) other sleep disorders [11]. The diagnosis of these sleep disorders is based on subjective measures, such as sleep diaries, interview, sleep consultation, and questionnaires, as well as objective measures, such as polysomnography (PSG) and

Abbreviations: CI, confidence interval; DSM, diagnostic and statistical manual of mental disorders; EORTC, European organization for research and treatment of cancer; HNC, head and neck cancer; ICSD, international classification of sleep disorders; MDASI-HN, MD Anderson symptom inventory – head and neck module; OSA, obstructive sleep apnea; PSG, polysomnography; PSQI, Pittsburgh sleep quality index.

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actigraphy [12]. Among these distinct types of sleep disturbances, insomnia, hypersomnolence, and sleep-related breathing disturbances are expected to be commonly experienced by HNC patients.

Firstly, insomnia entails difficulties falling or staying asleep or sleep of poor quality, leading to daytime disabilities [13]. Insomnia is the most common type of sleep disturbances among the general population [12]; this problem is even more prevalent in cancer patients [14]. Secondly, hypersomnolence is characterized by excessive daytime sleepiness and only diagnosed in the absence of other sleep disorders which might cause insufficient sleep and hence more sleepiness during the day. However, in cancer patients hypersomnolence is often reported as a symptom while the exact cause is unknown [15]. Factors found to be related to hypersomnolence are, for example, radiotherapy, chemotherapy, and opiates (i.e., a commonly prescribed pain-relieving medication among HNC patients) [16–19]. Finally, obstructive sleep apnea (OSA), one of the most prominent form of sleep-related breathing disturbances, involves frequent breathing pauses due to narrow or obstructed upper airways [20]. HNC patients are at risk for this condition because the pharyngeal and craniofacial structures are often altered due to cancer itself or its treatment side effects.

Despite its importance, precise estimates of the prevalence of sleep disturbances among HNC patients are lacking [21]. Previous reviews reported prevalence rates ranging from 8% to 100% among cancer patients [22–25]. To the extent of our knowledge, no meta-analysis has been performed on the prevalence of all different types of sleep disturbances among HNC patients. Therefore, the aim of this study is to systematically review the prevalence of all types of sleep disturbances among HNC patients before, during, and after treatment using meta-analysis approach.

Methods

Literature search

The search strategy was part of another systematic review which examined sleep disturbances among mixed cancer patients (Prospero ID CRD42018088119) [26]. A comprehensive search was performed in the following bibliographic databases: Pubmed, Embase, CINAHL, and PsycINFO. Databases were searched from inception up to November 2017. Synonyms and closely related words were searched as index terms or free-text words for the following terms: cancer (e.g., cancer, malignancy, and carcinoma), sleep disturbances (e.g., sleep problems, disturbed sleep, parasomnia, hypersomnolence, and circadian rhythm disturbance), and epidemiological studies (e.g., epidemiological studies, cross-sectional, and observational). All terms related to distinct forms of sleep disturbance, based on the ICSD-3, as well as different index terms for each bibliographic database were listed. The complete description of our search strategy is available in Appendix 1.

An information specialist from the medical library (de Vries R) provided advice on the literature search. Additional relevant full-texts were hand-searched from the reference list of the included studies and relevant reviews.

Inclusion and exclusion criteria

Studies which met the following inclusion criteria were included in this systematic review: 1) measuring any type of sleep disturbances, 2) including HNC patients, 3) reporting the prevalence of sleep disturbances among HNC patients, and 4) full-text in English. Studies with all treatment modalities (surgery, radiotherapy, chemotherapy, combination, treatment with curative intent, or palliative treatment), phase of treatment (before, during, or after treatment), and any study design were included. Case-reports, narrative studies, study protocols, conference abstracts, editorials, and systematic reviews were excluded. The prevalence did not have to be the primary aim of the study.

Screening and selection of relevant articles

Two independent reviewers (Santoso AMM and Jansen F) each screened titles and abstracts after previously removing all duplicates from the search results. Titles and abstracts which were clearly not relevant (e.g., focusing on patients with benign tumors, non-adult populations, or animal studies) were excluded. Full-texts of the remaining references were retrieved. Subsequently, relevant full-texts were selected based on the inclusion and exclusion criteria. Disagreements were discussed and when necessary, a third reviewer (Verdonck-de Leeuw IM and/or van Straten A) was consulted until agreement was reached.

Data extraction and quality assessment

Both data extraction and quality assessment were performed by two independent reviewers (Santoso AMM and Jansen F). Any disagreements between raters were discussed and when necessary, a third reviewer (Verdonck-de Leeuw and/or van Straten A) was consulted until consensus was reached. We extracted information related to: study characteristics (i.e., publication year, country of study, study design, sample size, and eligibility criteria), population characteristics (i.e., demographics, cancer site and stage, and treatment characteristics), sleep disturbance measures (i.e., measurement instrument used and time point of measurement), and the prevalence of sleep disturbances (i.e., overall prevalence and prevalence among subgroups).

Each study was appraised for its methodological quality and potential bias. We used the critical appraisal checklist developed by the Joanna Briggs Institute [27]. In brief, this list consists of nine items examining the quality of studies which report prevalence, based on how the study was designed, conducted, and reported (Table 2, footnote). Each item is answered with yes, no, unclear (i.e., when some information is not reported in the article), or not applicable (i.e., when the question is not applicable to a certain study design). We calculated the total quality score for each study based on the total number of positively scored items. For the third item in this list ('Was the sample size adequate?'), we used a recommended formula to calculate minimum sample size in prevalence studies [28]. Using this formula, the minimum sample size was 289 participants [28,29].

Analyses

Pooled means of prevalence rates were calculated using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood 2013). For each of the sleep disturbances, the pooled prevalence rate was calculated using a random effects model because it was expected that the studies would be methodologically heterogeneous [29]. Heterogeneity was visually examined by inspecting the forest plots and statistically confirmed by examining the I^2 values. An I^2 value of 0% indicates no observed heterogeneity among studies, 1–25% indicates low heterogeneity, 25–75% indicates moderate heterogeneity, and >75% indicate high heterogeneity [30]. A confidence interval of 95% was used. We also examined the prevalence rate in a set of pre-defined groups, namely: type of treatment (surgery, chemotherapy, or (chemo-) radiotherapy; single therapy or multimodal therapy), phase of treatment (before, during, or after), measurement instrument used (i.e., among different types of questionnaire or different cut-offs), and studies with a high quality (risk of bias assessment $\geq$ 5 items

evaluated positive). Funnel plots were generated to visually examine the presence of publication bias, which was then statistically tested by Egger's regression test and Begg–Mazumdar's rank correlation test. When publication bias seemed to be present (p-value < 0.05), Duval–Tweedie's trim-fill test was performed to calculate the adjusted pooled estimates. Reporting of meta-analyses was performed according to PRISMA guidelines (Appendix 2) [31].

Results

Inclusion of studies

The search resulted in 7191 records (Fig. 1). The majority of the records were excluded based on title and abstract screening. Full-texts were retrieved for the remaining 87 references. Of these 87 records, 26 articles fulfilled the eligibility criteria and three additional relevant full-texts were found during hand-searching. This resulted in 29 full-texts of accumulatively 2315 HNC patients included in this review.

Characteristics of the included studies

The majority (72%) of these studies had a cross-sectional design [32–52]. The remaining studies had prospective observational [53] or retrospective design [54–58]. Most studies (59%) were conducted in the USA, Canada, or European countries [34,35,37,39–41,43,45–48,50,52,54,57,59,60]. Twenty-one studies focused specifically on HNC patients [32,34–36,39–42,44–46,48,50,51,53–56,58–60], while eight studies focused on mixed cancer diagnoses but included a separate analysis among HNC patients. Nineteen studies (66%) primarily aimed to measure sleep disturbances [32–36,41,42,44–48,50,51,53,55–57,60], while the remaining studies aimed to measure various symptoms [37–39,43,49,52,54,59], quality of life [40], or psychiatric disorders [58]. The majority of the studies included HNC patients of mixed or

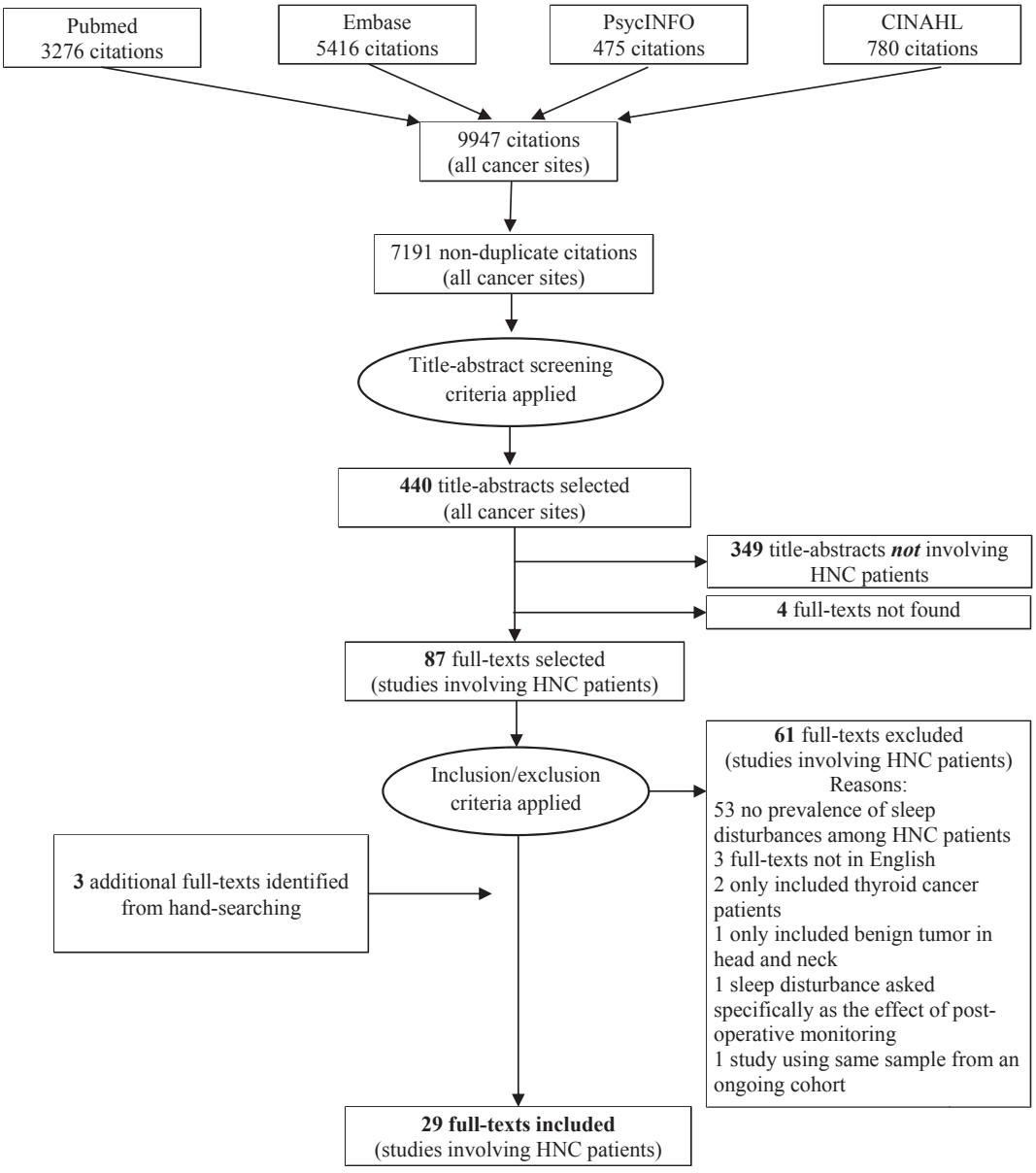

Fig. 1. Flow diagram of the literature search and selection.

unspecified site [33–35,37–39,41,43,44,46–50,52,54,57–60] while the remaining included HNC patients of specific location, such as tongue [32,40], larynx [42,51], nasopharynx [53,55,56], and oropharynx [45]. About 33% [36] up to 93% [51] of the study population consists of male HNC patients, while the gender proportion was unknown among eight studies [33,37,38,43,47,49,52,57].

Among the 29 included studies, 10 studies (34%) measured more than one types of sleep disturbances [33,34,36,39,40,44,45,50,51,59]. The included studies used a variety of definitions and instruments to report on sleep disturbances. The studies were grouped into three categories. The first category was insomnia and consisted of 17 studies [33,34,37,39,40,43–45,47,49,52,54–59]. The studies used either self-reported insomnia symptoms (including poor sleep quality, disturbed sleep, and trouble falling asleep) as well as interview- and diagnostic and statistical manual of mental disorders (DSM)-based insomnia diagnosis. Self-reported insomnia symptoms were measured by questionnaires in 14 studies, of which four studies used the Pittsburgh sleep quality index (PSQI) with various cut-off scores [34,44,55,56], two studies used MD Anderson symptom inventory – head and neck module (MDASI-HN) [39,59], two studies used the European organization for research and treatment of cancer (EORTC) questionnaire [43,52], one study used the Hamilton depression inventory [47], and five studies used either a study-specific questionnaire or used a known questionnaire but did not report the cut-off score [37,40,45,49,54]. One study used multiple definitions of self-reported insomnia symptoms (i.e., insomnia measured by insomnia severity index [ISI] with unknown cut-off and poor sleep quality measured by PSQI with cut-off of 5) [33]. The DSM-based diagnosis of insomnia was measured by structured interview in two studies [57,58].

The second category was hypersomnolence and consisted of 12 studies [33,34,36,38–40,44,45,49–51,59]. Studies on excessive daytime sleepiness and drowsiness were included in this category. A slight majority of the studies (58%) used the Epworth sleepiness scale (ESS) to measure daytime sleepiness, although with various cut-offs or without pre-defined cut-off scores [33,34,36,44,45,50,51]. The remaining studies used various instruments to measure drowsiness, namely the MDASI-HN [39,59], Edmonton symptom assessment scale [38,49], or Memorial symptom assessment scale [40].

The third category was sleep-related breathing disturbances and consisted of 14 studies [32,34–36,41,42,44–46,48,50,51,53,60]. We included studies on OSA and OSA-related symptoms into this category. Polysomnography (PSG) was used in the majority of studies ($n = 10$, 71%) [32,34–36,42,46,48,51,53,60] to establish the diagnoses, while three studies used home sleep testing [41,45,50]. Questionnaires and interviews were used to measure symptoms such as snoring and choking/gasping during sleep [44–46,50].

We found no studies reporting on the prevalence of the remaining types of sleep disturbances, such as circadian rhythm sleep–wake disorder, parasomnia, or sleep-related movement disorders.

Three studies did not report details related to treatment phase [37,38,43]. Among the studies that provided details on treatment phase, three studies reported sleep disturbances before the start of treatment [39,56,60], two studies during treatment [33,47], 12 studies after treatment [32,35,36,40–42,44–46,48,50,51], five studies included patients who were either before or after treatment [53,55,57–59], and two studies reported sleep disturbances among patients who are undergoing treatment or who have finished their treatment [34,52]. In general, these studies included patients with curative treatment, although not all studies provided detailed information on treatment intent. Three studies reported sleep disturbances during palliative treatment [49,52,54]. More details on the characteristics of the included studies are presented in Table 1.

Quality and risk of bias assessment

The quality and risk of bias assessment is presented in Table 2. Only one study (3%) had a sufficient sample size (i.e., ≥289 participants) [39]. A majority of the studies (86%) had a sample size of less than 100 HNC patients [32–36,38,40–53,55–58,60]. Two studies (7%) scored positive on the item about response rate [39,53]. The remaining studies scored negative as they had a response rate of less than 70% and did not report on the characteristics of non-responders versus responders, which hampers the ability to assess whether non-response might have affected the prevalence rate. Nineteen studies (66%) used validated sleep disturbance instruments or established diagnosis criteria of sleep disturbance [32,33,36,38,39,41,42,44,46,48,49,51,53,55–60], while the remaining studies used either study-specific questionnaires or instruments not specifically validated to measure sleep disturbances. Seventeen studies (59%) performed appropriate statistical analysis [32,35,41,42,44–48,50,51,53–55,57,58,60] which is defined as providing correct prevalence rates including the total number of patients screened on sleep disturbances and the actual number of patients with sleep disturbances. On average, studies had three positively marked items, ranging from one [34] to five [39,41,52,55,56,58,59].

Prevalence of insomnia

The pooled prevalence of insomnia was 29%, 45%, and 40% before, during, and after curative treatment, respectively (Table 3). During palliative care, the pooled prevalence is 52%. Before and after treatment, the prevalence of self-reported symptoms of insomnia was 30% and 46%, respectively, while the prevalence of a DSM-based diagnosis of insomnia disorder was 21% and 23%, respectively. When self-reported insomnia was defined with PSQI cut-off of 5, the pooled prevalence was 37% before and 75% after treatment. The comparison of pooled prevalence rates after different type of treatments was not possible since only two studies reported the prevalence rates after surgery only and one study reported the prevalence after chemotherapy only; the remaining studies were performed among HNC patients after various combinations of treatment.

Prevalence of hypersomnolence

The pooled prevalence of hypersomnolence was 16% before and 32% after curative treatment (Table 4). The prevalence rate of hypersomnolence during curative and palliative treatment was reported by each one study, which was 35% and 86%, respectively. When defined with ESS cut-off of 10, the pooled prevalence of sleepiness was 39%. The pooled prevalence of drowsiness measured by various instruments was 21%.

Prevalence of sleep-related breathing disturbances

The pooled prevalence of sleep-related breathing disturbances was 66% before and 51% after curative treatment (Table 5). No study reported the prevalence of sleep-related breathing disturbance during either curative or palliative treatment. After treatment, the pooled prevalence was 71% (apnea–hypopnea index [AHI] cut-off score of 5), 47% (AHI cut-off score of 15), and 37% (when defined as snoring). With respect to treatment modality, the pooled prevalence rate was 67% among patients who underwent surgery with (chemo-) radiotherapy, 58% among patients who underwent surgery alone, and 50% among patients who underwent chemo-radiotherapy only.

Table 1
Overview of included studies (ordered alphabetically by first author's name).

Author, year	Country	Design	Primary aim	HNC site	*n*	Age (years)	Men (%)	Time since diagnosis, treatment type and phase (at baseline)	Type of sleep disturbance, used measurement instrument, and cut-off score
Chan et al., 2012 [32]	Taiwan	Cross-sectional	Determine the prevalence of OSA in patients with primary squamous cell carcinoma of the tongue who underwent resection and/or RT.	Tongue	26	Mean 52 (32–71)	92	6 mo to 11 y after treatment. Neck dissection 85%, RT 65%	OSA, PSG, AHI $\geq$ 5
Echchikhi et al., 2017 [33]	Morocco	Cross-sectional	Determine prospectively the prevalence of sleep disorders, especially insomnia among patients with cancer receiving chemo and/or RT.	Unspecified[a]	41	Specific for HNC is not reported		Undergoing treatment. Surgery, chemo, RT and endocrine therapy.	Insomnia, ISI, cut-off unknown Poor sleep quality, PSQI $\geq$ 5 Sleepiness, ESS, cut-off unknown
Faiz et al., 2014 [34]	USA	Cross sectional	Describe characteristics of sleep disorders in patients with HNC referred for evaluation based on PSG data; determine the risk factors and symptoms that suggest underlying sleep-related breathing disorder	Unspecified	56	60 (28–87)	77	<5 y after diagnosis or currently undergoing treatment 80%. Prior RT 79%	Poor sleep quality, PSQI > 8 OSA, PSG, AHI > 5 Sleepiness, ESS $\geq$ 10
Friedman et al., 2001 [35]	USA	Cross sectional	Identify incidence of OSA in patients with HNC treated by surgical resection and compare it with general population.	Tongue base, pharynx or supraglottic larynx	24	Mean 65 (39–83)	88	After surgery 100%, received RT 42%	OSA, PSG, RDI > 15
Gilat et al., 2013 [36]	Israel	Cross-sectional	Evaluate quality of sleep and the rate of sleep-disordered breathing in patients treated for tongue cancer with radial forearm free flap reconstruction.	Tongue	15	Mean 57 (27–79)	33	Mean time from treatment completion (including postoperative therapy): 4.9 y (range 2–6 y). After surgery (tongue dissection and elective neck dissection) = 100%.	OSA, PSG, AHI > 5 Sleepiness ESS $\geq$ 8
Grond et al., 1993 [54]	Germany	Prospective observational	Assess the causes and mechanisms of pain and to evaluate the efficacy and side effects of the pain relief among HNC patients.	Nose, paranasal sinuses, nasopharynx, oropharynx, salivary glands, hypopharynx, larynx or other sites of the head	167	58 ± 11	70	Before pain treatment (100%). Undergone RT 80%, undergone surgery 63%, undergone chemo 41%, received no anticancer treatment 9%. Palliative anticancer treatment 32%, exhausted oncologic options/no benefit anticipated from further treatment 68%	Insomnia, unspecified computerized form to measure the frequency of symptoms.
Grond et al., 1994 [37]	Germany	Cross-sectional	Evaluate the prevalence of 15 important symptoms and symptom groups in cancer of different sites.	Unspecified[a]	236	Specific for HNC is not reported		At time of referral to the pain clinic for treatment of "intractable" pain. Treatment phase for HNC subsample not reported, but the majority of all cancer patients is palliative.	Insomnia, unspecified questionnaire
Gunn et al., 2013 [59]	USA	Cross-sectional[b]	Examine the pattern of symptoms experienced by patients with HNC before planned RT or CRT	Unspecified	270	Median 59 (SD 11.9)	76	Median days from last day chemo 21.6 (SD 25.3), from surgery to completion of MDASI-HN: 39.1 d (SD 25.7). Before starting curative RT-based treatment (100%). Prior chemo 26.7%, prior surgery 29%.	Disturbed sleep MDASI-HN $\geq$ 5 (moderate to severe) Drowsiness MDASI-HN $\geq$ 5 (moderate to severe)

Gupta et al., 2016 [38]	India	Cross-sectional	Assess presence and severity of various symptoms among critically ill cancer patients at the time of admission to an intensive care unit.	Unspecified[a]	26	Specific for HNC is not reported		Not reported	Drowsiness ESAS, cut-off unknown
Hanna et al., 2015 [39]	USA	Cross-sectional	Assess and explore symptom severity and interference in treatment-naive HNC patients.	Unspecified	748	Median 59 (SD 14.6)	68	Had no prior cancer therapy (100%)	Disturbed sleep MDASI-HN $\geq$ 5 (moderate to severe) Drowsiness MDASI-HN $\geq$ 5 (moderate to severe)
Harrison et al., 1997 [40]	USA	Cross-sectional	Evaluate quality of life in patients treated with primary RT for cancer of the base of tongue.	Base of tongue	29	58 (35–71)	81	Median follow-up 5 y (min. 3 y). After curative RT (100%),	Insomnia, MSAS, cut-off unknown Drowsiness, MSAS, cut-off unknown
Huyett et al., 2017 [41]	USA	Cross-sectional	Assess the prevalence of OSA in HNC patients treated with RT or CRT for laryngeal or oropharyngeal primary tumor sites.	Larynx or oropharynx	16	62 (48–75)	81	>3 mo after RT or CRT (100%), no active or recurrent disease	OSA, HST, AHI $\geq$ 5
Israel et al., 2006 [42]	Brazil	Cross-sectional	Assess occurrence and severity of OSA in patients undergoing laryngectomy for the treatment of laryngeal carcinoma.	Larynx	22	Mean 66 (50–80)	91	Underwent laryngectomy in the last 6 y (100%)	OSA, PSG, AHI $\geq$ 15, moderate to severe
Johnsen et al., 2009 [43]	Denmark	Cross-sectional	Measure symptoms and problems in advanced cancer patients and identify the predictors.	Unspecified[a]	72	Specific for HNC is not reported		Diagnosis/treatment information specific for HNC is not reported	Insomnia, EORTC-C30 $\geq$ 33.3
Li et al., 2017 [44]	Japan	Cross-sectional	Provide a detailed description of the characteristics of sleep disturbance in long-term HNC survivors.	Unspecified	77	Mean 68 (28–86)	68	$\geq$3 y after surgical treatment (100%)	Poor sleep quality, PSQI $\geq$ 5 and PSQI $\geq$ 8 Snoring, PSQI Sleepiness, ESS $\geq$10
Lin et al., 2014 [53]	Taiwan	Retrospective	Assess changes in respiratory sleep indexes, sleep architecture, and daytime somnolence before and after treatment in patients with nasopharyngeal cancer.	Nasopharynx	18	Mean 50	83	Before curative treatment (Chemo) RT = 100%	OSA, PSG, AHI $\geq$ 5, AHI $\geq$ 15 (moderate or severe)
Loth et al., 2017 [45]	France	Cross-sectional	Evaluate the rate of OSA in a population of patients treated for an advanced oropharyngeal cancer.	Oropharynx	51	Mean 6 (44–76)	73	$\geq$12 mo post treatment. Combined chemo 80%, surgery and CRT 20%. Mean time between end of treatment and sleep disturbance measurement 54 mo, (20–84 mo)	Trouble falling asleep, sleep consultation OSA, HST AHI > 10 Sleepiness, ESS $\geq$ 10
Mo et al., 2014 [55]	China	Prospective observational	Explore cognitive function, and prevalence of depression, anxiety and sleep changes in nasopharyngeal carcinoma patients.	Nasopharynx	51	Mean 40 (24–60)	63	After diagnosis (before treatment started) = 100%	Poor sleep quality, PSQI > 5
Nesse et al., 2006 [46]	The Netherlands	Cross-sectional	Identify the prevalence of OSA within a Dutch population of patients treated for HNC.	Oral or oropharynx	33	Mean 62 (38–87)	70	6-mo to 5 y post curative treatment (100%). Surgery 39%, Surgery and RT 39%, RT 22%	OSA, PSG AHI $\geq$ 5 OSA-related complaints, ESS $\geq$ 10 or $\geq$2 study-specific items
Palesh et al., 2010 [47]	USA	Cross-sectional	Determine prospectively the prevalence of insomnia among patients with cancer receiving chemo.	Unspecified[a]	4	Specific for HNC is not reported		Starting chemo (100%)	Clinical insomnia HDI, cut-off based on DSM-IV
Payne et al., 2005 [60]	Canada	Cross-sectional[b]	Determine the prevalence of OSA among patients with malignant tumors of the oral cavity and oropharynx prior to primary surgical resection.	Oral cavity or oropharynx	17	64 ± 2	82	Before surgery (100%), range 2–14 d	OSA, PSG AHI $\geq$ 15

(*continued on next page*)

Table 1 (*continued*)

Author, year	Country	Design	Primary aim	HNC site	*n*	Age (years)	Men (%)	Time since diagnosis, treatment type and phase (at baseline)	Type of sleep disturbance, used measurement instrument, and cut-off score
Qian et al., 2010 [48]	Canada	Cross-sectional	Determine the point prevalence of sleep apnea in patients following oral and oropharyngeal cancer treatment	Oral or oropharynx	24	Mean age surgical group 64, nonsurgical group 55	67	≥6 mo after completion primary treatment; no residual or recurrent disease (100%)	OSA PSG RDI ≥ 15 (moderate and severe) OSA PSG RDI ≥ 5 (all severity)
Qin et al., 2015 [56]	China	Prospective observational	Examine sleep and psychological characteristics in patients with local-advanced nasopharyngeal carcinoma following IMRT completion and concurrent chemo.	Nasopharynx	60	39.8 ± 8.9	62	After diagnosis, before IMRT started (100%); (2 cycles concurrent chemo 33%, 3 cycles of concurrent therapy 67%)	Poor sleep quality, PSQI > 5
Savard et al., 2011 [57]	Canada	Prospective observational	Assess the prevalence and natural course of insomnia comorbid with cancer during an 18-month period in patients undergoing treatment for non-metastatic cancer	Unspecified[a]	59	Specific for HNC is not reported		Before curative surgery (100%)	Insomnia symptoms, IIS based on DSM-IV criteria
Shao et al., 2016 [49]	China	Cross-sectional	To identify prevalence and severity of non-pain symptoms and to clarify possible influences on each non-pain symptom.	Unspecified[a]	14	Specific for HNC is not reported		Palliative 100%, immediately after admission to hospital	Insomnia, study-specific scale, cut-off unknown Drowsiness, ESAS, cut-off unknown
Steffen et al., 2009 [50]	Germany	Cross-sectional	Assess the prevalence of OSA in HNC patients following surgical treatment.	Unspecified	31	OSA patients 67 (59–77), non-OSA patients 64 (48–77)	71	Within 2 y of last aftercare visit, but more than 6 mo after last surgical and/or adjuvant therapy.	OSA, HST AHI ≥ 20 snoring, interview Sleepiness, ESS ≥ 10
Teixeira et al., 2013 [51]	Brazil	Cross-sectional	Compare the prevalence and severity of OSA in patients undergoing laryngectomy.	Larynx	14	68 (41–84)	93	After partial laryngectomy (100%), mean time after end of treatment 54 mo (6–84 mo)	OSA, PSG AHI 5–30 (mild) OSA, PSG AHI > 30 (severe) OSA, PSG AHI > 5 (all severity) Sleepiness, ESS > 10
Unal et al., 2016 [58]	Turkey	Prospective observational	Evaluate the effects of RT on psychiatric disorder in HNC patients.	Unspecified	51	57.6 ± 11.2	90	Before RT	Sleep disorder, interview DSM-IV
van den Beuken-van Everdingen et al., 2009 [52]	The Netherlands	Cross-sectional	To measure the prevalence of non-pain physical symptoms and psychological symptoms in patients with cancer.	Unspecified[a]	63	Specific for HNC is not reported		Curative 62% (of which 64% >6 mo after treatment, 36% current/≤6 mo after curative treatment); palliative 38%	Trouble sleeping EORTC-C30 score 3 (moderate) or 4 (severe)

Abbreviations: AHI: apnea–hypopnea index; Chemo: chemotherapy; CRT: chemoradiotherapy; DSM-IV: diagnostic and statistical manual of mental disorders, fourth edition; EORTC: European organization for research and treatment of cancer; ESAS: Edmonton symptom assessment scale; ESS: Epworth sleepiness scale; HDI: Hamilton depression inventory; HNC: head and neck cancer; HST: home sleep test; IIS: insomnia interview schedule; IMRT: intensity modulated radiotherapy; ISI: insomnia severity index; MDASI-HN: MD Anderson symptom inventory – head and neck module; MSAS: Memorial symptom assessment scale; OSA: obstructive sleep apnea; PSG: polysomnography; PSQI: Pittsburgh sleep quality index; RDI: respiratory disturbance index; RT: radiotherapy; SD: standard deviation.

Note: Age was denoted in mean ± standard deviation (SD) or median (range), otherwise noted. All percentages are rounded.

[a] The study focused on mixed cancer patients. Sleep disturbances among head and neck cancer (HNC) patients were reported.

[b] Original study design is prospective observational, sleep analysis is performed at one study point (cross-sectional).

Table 2
Quality and risk of bias appraisal of included studies (ordered alphabetically by first author's name).

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Total positive score
Chan et al., 2012 [32]	Y	U	N	N	U	Y	U	Y	U	3
Echchikhi et al., 2017* [33]	N	Y	N	N	U	Y	Y	N	U	3
Faiz et al., 2014 [34]	N	Y	N	N	U	U	N	N	N	1
Friedman et al., 2001 [35]	Y	N	N	N	U	U	U	Y	U	2
Gilat et al., 2013 [36]	Y	Y	N	Y	U	Y	U	N	U	4
Grond et al., 1993 [54]	Y	Y	N	N	U	U	U	Y	U	3
Grond et al., 1994* [37]	Y	Y	N	U	U	U	U	N	U	2
Gunn et al., 2013 [59]	Y	Y	N	Y	U	Y	Y	N	U	5
Gupta et al., 2016* [38]	Y	U	N	U	U	Y	N	N	U	2
Hanna et al., 2015 [39]	Y	U	Y	Y	Y	Y	U	N	NA	5
Harrison et al., 1997 [40]	U	U	N	Y	U	U	Y	N	U	2
Huyett et al., 2017 [41]	Y	U	N	Y	U	Y	Y	Y	U	5
Israel et al., 2006 [42]	Y	U	N	Y	U	Y	U	Y	N	4
Johnsen et al., 2009* [43]	Y	N	N	U	U	U	Y	N	N	2
Li et al., 2017 [44]	N	N	N	N	U	Y	U	Y	U	2
Lin et al., 2014 [53]	N	U	N	N	Y	Y	Y	Y	NA	4
Loth et al., 2017 [45]	Y	Y	N	Y	U	U	U	Y	U	4
Mo et al., 2014 [55]	N	U	N	Y	U	Y	Y	Y	Y	5
Nesse et al., 2006 [46]	N	Y	N	Y	U	Y	U	Y	N	4
Palesh et al., 2010* [47]	Y	U	N	U	U	U	Y	Y	U	3
Payne et al., 2005 [60]	Y	N	N	N	U	Y	Y	Y	U	4
Qian et al., 2010 [48]	Y	U	N	Y	U	Y	U	Y	N	4
Qin et al., 2015 [56]	Y	Y	N	Y	U	Y	U	N	Y	5
Savard et al., 2011* [57]	N	U	N	U	U	Y	Y	Y	U	3
Shao et al., 2016* [49]	N	Y	N	N	U	Y	Y	N	U	3
Steffen et al., 2009 [50]	Y	Y	N	N	U	U	U	Y	U	3
Teixeira et al., 2013 [51]	Y	Y	N	Y	U	Y	U	Y	N	5
Unal et al., 2016 [58]	Y	U	N	Y	U	Y	Y	Y	U	5
van den Beuken-van Everdingen et al., 2009* [52]	Y	U	N	U	U	U	Y	N	U	2

Note:
1. Q1–9: questions to assess study quality and risk of bias, as listed below
Q1: Was the sample frame appropriate to address the target population?
Q2: Were study participants sampled in an appropriate way?
Q3: Was the sample size adequate?
Q4: Were the study subjects and the setting described in detail?
Q5: Was the data analysis conducted with sufficient coverage of the identified sample?
Q6: Were valid methods used for the identification of the condition?
Q7: Was the condition measured in a standard, reliable way for all participants?
Q8: Was there appropriate statistical analysis?
Q9: Was the response rate adequate, and if not, was the low response rate managed appropriately?
2. Y, yes, highlighted; N, no; U, unclear; NA, not applicable.
3. Studies marked with asterisk (*) focused on mixed cancer patients, but sleep disturbances among head and neck cancer patients were reported. For these studies the items "Were the study subjects and the setting described in detail?" and "Was the data analysis conducted with sufficient coverage of the identified sample?" were scored as "Unclear".

Publication bias

Publication bias was examined on the prevalence of insomnia during treatment (p-value > 0.05), insomnia after treatment (p-value < 0.05), and sleep-related breathing disturbances after treatment (p-value < 0.05). Random effects model of Duval–Tweedie's test resulted in the adjusted pooled estimates of 50% for insomnia during treatment, 47% for insomnia after treatment, and 40% for sleep-related breathing disturbances after treatment (Tables 3 and 5). We did not examine publication bias on the other sleep disturbances before and after treatment because the number of studies was too small (i.e., less than three studies).

Discussion

In this systematic review and meta-analysis investigating the prevalence of sleep disturbances among HNC patients, we found 29 studies measuring three types of sleep disturbances: insomnia, hypersomnolence, and sleep-related breathing disturbances. No studies were found investigating circadian rhythm sleep–wake disorders, parasomnias, or sleep-related movement disorders, despite our extensive search strategy. The pooled prevalence of insomnia was 29% before treatment, 45% during treatment (50% after correcting for publication bias), and 40% after treatment (47% after correcting for publication bias). The pooled prevalence of hypersomnolence was 16% before and 32% after treatment. For sleep-related breathing disturbances, the pooled prevalence was 66% before and 51% after treatment (40% after correcting for publication bias). Only one study reported the prevalence of HNC patients who had both sleep-related breathing disturbance and hypersomnolence [45], hence we were unable to confirm whether the prevalence rate of hypersomnolence overlaps with that of sleep-related breathing disturbance.

The prevalence of sleep disturbances before the start of HNC treatment (16–66%) is notably higher compared to that of the general population (2–38%) [61,62]. Tumor mass effect of HNC may cause obstruction around tongue, pharynx, and epiglottis, the most common sites involved in OSA [63]. In addition, anxiety and depression are highly prevalent at the time of HNC diagnosis [8,9] which may also contribute to insomnia. People recently confronted with the diagnosis of HNC may experience fear and uncertainty related with HNC treatment and its outcome [64]. Such uncertainty may affect their social situations and sleep–wake patterns. Furthermore, two major risk factors of HNC, alcohol

Table 3
Prevalence rates of insomnia.

Characteristics	N study	Cumulative rates	Pooled estimate[a]	95% CI[a]	Heterogeneity		
					I^2	Q-stats	*p*-value
Before treatment, all [39,55–59]	6	355/1093	0.29	0.20–0.41	86.16	36.12	<0.001
Study design							
• Good quality studies (≥5 positive items) [39,55,56,58,59]	5	326/1034	0.26	0.16–0.38	86.3	29.19	<0.001
Definition of insomnia							
• Self-reported insomnia, all [39,55,57,59]	4	323/983	0.30	0.21–0.41	82.48	17.12	0.001
◦ Poor sleep quality: PSQI > 5 [55,56]	2	41/111	0.37	0.29–0.46	0	0	1
◦ Disturbed sleep: MDASI-HN ≥ 5 [39,59]	2	282/872	0.25	0.11–0.48	93.9	16.39	<0.001
• DSM-based diagnosis of insomnia [57,58]	2	33/110	0.21	0.02–0.80	94.49	18.15	<0.001
During treatment, all [33,47,52]	3	26/59	0.45	0.33–0.58	0	1.39	0.500
Adjusted estimates (publication bias)[b]	NA	NA	0.50	0.38–0.61	NA	NA	NA
After treatment, all [40,44,45,52,55,57–59]	8	168/395	0.40	0.24–0.58	89.35	65.73	<0.001
Study design							
• Good quality studies (≥5 positive items) [55,58,59]	3	50/173	0.25	0.05–0.67	94.81	38.50	<0.001
Definition of insomnia							
• Self-reported insomnia, all [40,44,45,52,55,59]	6	144/304	0.46	0.28–0.65	88.86	44.89	<0.001
◦ PSQI ≥ 5 [44,55]	2	97/128	0.75	0.54–0.89	80.92	5.24	0.022
• DSM-based diagnosis of insomnia [57,58]	2	24/91	0.23	0.03–0.78	92.34	13.06	<0.001
Treatment type							
• Surgery only [57,59]	2	33/114	0.31	0.09–0.67	94.81	38.5	0.004
• Single treatment[c] [55,57,59]	3	66/162	0.43	0.16–0.75	92.20	25.63	<0.001
Adjusted estimates (publication bias)[b]	NA	NA	0.47	0.28–0.66	NA	NA	NA
Palliative care, all [49,52]	2	16/38	0.52	0.04–0.97	92.32	13.02	<0.001
Unknown phase of treatment, all [37,43]	2	182/308	0.54	0.34–0.73	89.79	9.80	0.002

Abbreviations: CI, confidence interval; DSM, diagnostic and statistical manual of mental disorders; MDASI-HN, MD Anderson symptom inventory – head and neck module; NA, not applicable; PSQI, Pittsburgh sleep quality index.
Note:
[a] Pooled estimate and 95% CI were analyzed using random effects model.
[b] Adjusted values generated using Duval–Tweedie's trim and fill test, random effects model.
[c] Single treatment including either surgery only or chemotherapy only.

Table 4
Prevalence rates of hypersomnolence.

Characteristics	N study	Cumulative rates	Pooled estimate[a]	95% CI[a]	Heterogeneity		
					I^2	Q-stats	*p*-value
Before treatment, all [39,59]	2	177/872	0.16	0.07–0.32	88.78	8.91	0.003
After treatment, all [36,40,44,45,50,51,59]	7	90/275	0.32	0.20–0.48	80.40	30.61	<0.001
Study design							
• Good quality studies (≥5 positive items) [51,59]	2	13/85	0.18	0.07–0.38	58.36	2.40	0.121
Definition of hypersomnolence							
• Sleepiness: ESS ≥ 10 [44,45,50,51]	4	64/148	0.39	0.23–0.58	71.81	10.64	0.014
• Drowsiness [40,59]	2	19/100	0.21	0.07–0.49	82.91	5.85	0.016
Treatment type							
• Surgery only [51,59]	2	10/88	0.15	0.04–0.45	77.83	4.51	0.034
• Single treatment[b] [51,59]	2	11/85	0.18	0.07–0.38	58.36	2.40	0.121

Abbreviations: CI, confidence interval; ESS, Epworth sleepiness scale.
Note:
[a] Pooled estimate and 95% CI were analyzed using random effects model.
[b] Single treatment including either surgery only, chemotherapy only or radiotherapy only.

abuse and tobacco smoking, might play a role in the high prevalence of sleeping disturbances among HNC patients. Heavy alcohol users often experience insomnia even after they stop their alcohol consumption [65], while smokers suffer more insufficient sleep compared to non-smokers [66]. Moreover, smoking damages oropharyngeal mucosal structure [67] and this may contribute to the relationship of smoking with sleep-related breathing disturbances in patients with HNC.

The evidence on the high prevalence of sleep disturbances during treatment was based on only two studies investigating insomnia [49,52] and one study investigating hypersomnolence [33], with pooled prevalence of 45% and 35%, respectively. Cancer treatment is physically and psychologically burdensome for HNC patients due to the treatment-related side-effects. HNC patients who are undergoing (chemo-) radiotherapy often experience mucositis-related symptoms such as xerostomia and oral pain, as well as fatigue, drowsiness, and nausea [7,68]. These symptoms may cause circadian rhythm changes among HNC patients and may contribute to the high prevalence of insomnia and hypersomnolence during treatment. Moreover, one out of five HNC patients continues smoking or drinking alcohol during cancer treatment [69] which may worsen their sleep problems. Pain-relievers such as opioids are also often prescribed during cancer treatment and may result in sleep–wake rhythm changes [16,17]. So far, however, only a limited number of studies reported on the prevalence of sleep disturbances during HNC treatment, therefore warranting additional studies.

The prevalence rates of sleep disturbances after treatment were also high: 40%, 32%, and 51% on insomnia, hypersomnolence, and sleep-related breathing disturbances, respectively. This might be

Table 5
Prevalence rates of sleep-related breathing disturbances.

Characteristics	N study	Cumulative rates	Pooled estimate[a]	95% CI[a]	Heterogeneity		
					I^2	Q-stats	*p*-value
Before treatment, all[b] [53,60]	2	23/35	0.66	0.44–0.82	34.05	1.52	0.22
After treatment, all [32,34–36,41,42,44–46,48,50,51,53]	13	168/375	0.51	0.34–0.67	83.51	72.77	<0.001
Study design							
• OSA as exclusion criteria [32,36,41,45,48]	5	65/117	0.53	0.43–0.63	0	3.36	0.499
• Good quality studies (≥5 positive items) [41,51]	2	21/30	0.76	0.20–0.98	79.87	4.97	0.026
Definition of sleep-related breathing disturbances							
• OSA: AHI ≥ 5 [32,34,36,41,42,46,48,51,53]	9	139/205	0.71	0.48–0.86	83.76	49.25	<0.001
• OSA: AHI ≥ 15 [35,42,48,53]	4	37/68	0.47	0.34–0.61	56.42	6.89	0.076
• OSA: AHI ≥ 30 [42,45,51]	3	18/87	0.21	0.14–0.31	0	0.08	0.959
• Snoring [44,45,50]	3	57/159	0.37	0.09–0.77	94.97	39.77	<0.001
Treatment type							
• Surgery only [32,35,42,48,50,51]	6	45/93	0.58	0.30–0.82	76.83	21.58	0.001
• Chemoradiotherapy only [48,53]	2	14/27	0.50	0.33–0.76	47.82	1.92	0.166
• Surgery with (chemo)radiotherapy [32,35,48]	3	26/39	0.67	0.36–0.88	57.75	4.73	0.094
• Single treatment[c] [32,34,35,42,48,50,51]	7	84/137	0.65	0.37–0.85	81.48	32.4	<0.001
• Combination treatment[d] [32,35,45,48,53]	5	60/167	0.54	0.41–0.67	23.2	5.21	0.267
Adjusted estimates (publication bias)[e]	NA	NA	0.40	0.24–0.60	NA	NA	NA

Abbreviations: AHI, apnea–hypopnea index; CI, confidence interval; NA, not applicable; OSA, obstructive sleep apnea.
Note:
[a] Pooled estimate and 95% CI were analyzed using random effects model.
[b] Pooled prevalence of OSA defined with AHI ≥15.
[c] Single treatment including either surgery only, chemotherapy only or radiotherapy only.
[d] Combination treatment including chemoradiotherapy (with or without other modality) and surgery with either chemotherapy or chemoradiotherapy.
[e] Adjusted values generated using Duval–Tweedie's trim and fill test, random effects model.

related to HNC symptoms such as dry mouth complaints, lymphedema in the head and neck area, tinnitus, and dysregulation of thyroid hormone after (chemo-) radiotherapy. The high prevalence of insomnia may be associated with psychological symptoms such as depression, post-traumatic stress disorders, problems with body-image, and fear of cancer recurrence. These symptoms may continue to be present after HNC is treated successfully [64,70–73]. In addition, radiation in the head and neck area may be associated with sleep-related breathing disturbances in two ways: first, it may alleviate breathing disturbances by reducing the tumor mass; and on the other hand, it may cause scarring, airway narrowing, and alterations of the sensory- and mechanoreceptors in the upper airway [63].

We also found that more than a half of HNC patients receiving palliative care reported insomnia. This high prevalence of insomnia among patients in palliative care may be explained by the above-mentioned causes of sleep disturbances before, during, and after treatment of HNC, and further worsened by the advanced stage of cancer, cancer recurrence, distant metastasis or presence of a second primary cancer [73]. In addition, palliative care patients report high level of anxiety [49], which affects sleep quality.

The strength of this study is that meta-analytic methods were used to investigate the prevalence of various types of sleep disturbances among HNC patients. We also presented prevalence rates of sleep disturbances in different phases of treatment (i.e., before, during, and after treatment) and palliative care, which resulted in a thorough overview of studies performed so far.

We, however, also acknowledge some limitations of this study. Considerable heterogeneity was found regarding the definition of sleep disturbances, the used measurement instruments to assess sleep disturbances as well as the used cut-off scores on the measurement instruments. This heterogeneity was in line with previous reviews on the prevalence of sleep disturbances among mixed cancer patients and the general population [29,61]. In addition, only a limited number of studies were performed per subgroup of patients (e.g., regarding phase of treatment or type of treatment), which hindered the ability to statistically compare prevalence rates among these subgroups, as well as to examine differences among countries and study years. For example, it seems that among HNC patients, sleep-related breathing disturbances are more frequently present than other types of sleep disturbances but this observation needs further investigation. Also, we were only able to report the prevalence of hypersomnolence as a symptom, as there is lack of studies which reported hypersomnolence as a sleep disorder. Sleep disturbances, additionally, seem to increase after treatment, but longitudinal studies investigating the course of sleep disturbances from diagnosis to follow-up are needed to confirm this observation. Another limitation is that publication bias is likely to have occurred, which may either under- or overestimate the reported prevalence rates in this meta-analysis. We also excluded non-English articles, which may have resulted in underrepresentation of prevalence rates of sleep disturbances in non-English-speaking countries. Finally, most studies were of insufficient methodological quality: a small group of HNC patients were often included in the study, inadequate information on their participant recruitment were often provided, and non-validated instruments were often used to measure sleep disturbances.

Conclusion

This systematic review and meta-analysis demonstrated that sleep disturbances are highly prevalent at all HNC treatment phases, underlining the importance of early screening and tailored intervention for sleep disturbance among HNC patients. Further studies are essential to investigate the course of sleep disturbances from diagnosis to follow-up among both cancer survivors and patients in palliative care. Also, more insight is needed to understand the clinical, psychological, and life-style related factors associated with prevalence rates among different subgroups of HNC patients.

Practice points

1. The most commonly reported form of sleep disturbances among HNC patients are insomnia, hypersomnolence, and sleep-related breathing disturbances.
2. Sleep disturbances seem to be prevalent among newly diagnosed HNC patients, suggesting the importance of early screening for sleep disturbance already before treatment among this population.
3. Sleep disturbances remain to be prevalent during and after treatment, and are possibly associated with short-term and long-term treatment side effects. Healthcare professionals are therefore encouraged to include sleep disturbance assessment during HNC follow-up consultations.

Research agenda

1. Perform high quality longitudinal cohort studies with sufficient sample size on the course of sleep disturbances over time and factors that may cause or are associated with sleep disturbances among HNC patients over time, including sociodemographic (e.g., sex, age), clinical (e.g., metastasis to the brain, radiation in the head and neck area), and lifestyle factors (e.g., BMI, physical activity, and excessive smoking and alcohol consumption), as well as symptoms caused by cancer and its treatment.
2. More research on sleep disturbances among HNC patients is needed worldwide. Also, when resources are available, non-English literature should be reviewed on the prevalence of sleep disturbances among HNC patients.
3. Investigate possible innovations to tailor HNC treatment and its supportive care to prevent the progression of sleeping disturbances during and after HNC treatment.

Conflicts of interest

The authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2019.06.003.

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